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(72) GEISEN, Karl, DE
(71) HOECHST AKTIENGESELLSCHAFT, DE

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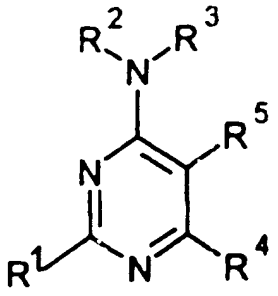
(30) 1997/03/13 (19710435.5) DE

(54) **UTILISATION DE DERIVES DE LA PYRIMIDINE, SEULS OU EN COMBINAISON AVEC D'AUTRES MESURES THERAPEUTIQUES, POUR LA PREVENTION DU CANCER**

(54) **USE OF PYRIMIDINE DERIVATIVES FOR THE PREVENTION OF CANCER, ON THEIR OWN OR IN COMBINATION WITH OTHER THERAPEUTIC MEASURES**



I

(57) Utilisation de dérivés de la pyrimidine, seuls ou en combinaison avec d'autres mesures thérapeutiques, pour la prévention du cancer. La présente invention porte sur l'utilisation de dérivés de la pyrimidine comme agents pour la prévention de problèmes de nature caminomateuse. Les dérivés de la pyrimidine sont des composés actifs de formule I (voir formule I), où R^1 à R^7 ont la signification spécifiée; leurs sels tolérables sur le plan physiologique.

(57) Use of pyrimidine derivatives for the prevention of cancer, on their own or in combination with other therapeutic measures The present invention is concerned with the use of pyrimidine derivatives as agents for the prevention of carcinomatous disorders. The pyrimidine derivatives used are active compounds of the formula I (see formula I), in which R^1 to R^7 have the meaning indicated, and their physiologically tolerable salts.

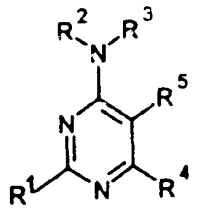
HOE 97/F 062

Abstract:

Use of pyrimidine derivatives for the prevention of cancer, on their own or in combination with other therapeutic measures

The present invention is concerned with the use of pyrimidine derivatives as agents for the prevention of carcinomatous disorders.

The pyrimidine derivatives used are active compounds of the formula I



I

in which R^1 to R^7 have the meaning indicated, and their physiologically tolerable salts.

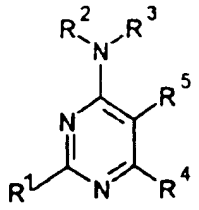
HOECHST AKTIENGESELLSCHAFT HOE 97/F 062 Dr. RU/pp

Description

Use of pyrimidine derivatives for the prevention of cancer, on their own or in combination with other therapeutic measures

The present invention is concerned with the use of pyrimidine derivatives as agents for the prevention of carcinomatous disorders.

The pyrimidine derivatives used are active compounds of the formula I



I

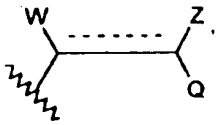
in which

R^1 is hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_6-C_{12})-aryl, (C_1-C_6)-alkoxycarbonyl-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-SO-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-SO_2-(C_1-C_6)-alkyl, dihydroxy-(C_1-C_6)-alkyl, aryl, heteroaryl, heteroaryl-(C_1-C_6)-alkyl, aryl-(C_1-C_6)-alkyl, (C_1-C_6)-alkoxycarbonylaryl, aryl-(C_1-C_6)-alkyloxy or heteroaryl-(C_1-C_6)-alkyloxy,

heteroaryl is pyridyl, furyl, tetrahydrofuryl, thienyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, benzothiazolyl;

where aryl and heteroaryl independently of one another can be substituted by one or more substituents selected from the group consisting of chlorine,

bromine, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, $-SO_2$-(C_1-C_6)-alkyl, hydroxy-(C_1-C_6)-alkyl, trifluoromethyl, or

R^1 is 

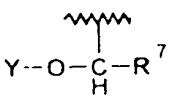
in which the dashed line is an optional double bond;

W, Q, Z independently of one another are H, (C_1-C_6)-alkyl, trifluoromethyl, phenyl, furyl, triazolyl, thiazolyl, thienyl, where phenyl, furyl, triazolyl, thiazolyl, thienyl independently of one another can be mono- to trisubstituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, trifluoromethyl, hydroxyl, or

R^1 is $-(C=O)-R^6$

R^6 is H, (C_1-C_6)-alkyl, aryl, heteroaryl

heteroaryl is pyridyl, furyl, tetrahydrofuryl, thienyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, benzothiazolyl; where aryl and heteroaryl independently of one another can be substituted by one to three substituents selected from the group consisting of chlorine, bromine, nitro, trifluoromethyl, (C_1-C_6)-alkoxy, -S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, $-SO_2$-(C_1-C_6)-alkyl, or

R^1 is 

R^7 is aryl, heteroaryl

heteroaryl is pyridyl, furyl, thienyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, quinolyl, where aryl and heteroaryl independently of one another can be substituted by one to three substituents selected from the group consisting of chlorine, bromine, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, -SO_2-(C_1-C_6)-alkyl;

R^2, R^3 independently of one another are hydrogen, (C_1-C_6)-alkyl, (C_6-C_{12})-aryl, (C_6-C_{12})-arylalkyl having 1 - 4 alkyl carbon atoms, where aryl can be substituted by one to three substituents selected from the group consisting of chlorine, bromine, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, or

R^2 and R^3, together with the nitrogen to which they are bonded, form the azetidino, pyrrolidino, piperidino, piperazino or morpholino group, where the heterocycles can be substituted by one or two substituents selected from the group consisting of chlorine, bromine, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, -SO_2-(C_1-C_6)-alkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, (C_1-C_6)-alkoxycarbonyl, N,N-(C_1-C_4)-dialkylcarbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, (C_6-C_{12})-arylcarbonyl substituted in the aryl radical by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_6-C_{12})-arylcarbonyl substituted in the aryl radical by (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_6-C_{12})-arylsulfonyl substituted in the aryl radical by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3, heteroarylcarbonyl or heteroarylsulfonyl;

R^4 and R^5 independently of one another are hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_6-C_{12})-aryl, naphthyl, furyl, where (C_6-C_{12})-aryl, naphthyl and furyl can be substituted by one or two substituents selected from the group consisting of chlorine, bromine, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, -SO_2-(C_1-C_6)-alkyl, hydroxyl;

and their physiologically tolerable salts.

Preferred compounds of the formula I are those in which

R^1 is cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy or (C_6-C_{12})-aryl;

R^4 and R^5 are hydrogen, halogen or trifluoromethyl;

R^2, R^3 independently of one another are hydrogen, (C_1-C_6)-alkyl, (C_6-C_{12})-aryl or (C_6-C_{12})-arylalkyl having 1 - 4 alkyl carbon atoms, or

R^2 and R^3, together with the nitrogen to which they are bonded, form the azetidino, pyrrolidino, piperidino, piperazino or morpholino group, or an azetidino, pyrrolidino, piperidino, piperazino or morpholino group substituted by identical or different groups R^6 and R^7;

R^6, R^7 are (C_1-C_6)-alkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, (C_1-C_6)-alkoxycarbonyl, N,N-(C_1-C_4)-dialkylcarbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, (C_6-C_{12})-arylcarbamoyl substituted in the aryl radical by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3, carbamoyl, (C_1-C_6)-alkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_6-C_{12})-arylcarbonyl substituted in the aryl radical by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_6-C_{12})-arylsulfonyl substituted in the aryl radical by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3,

heteroarylcarbonyl or heteroarylsulfonyl or one of the substituents R^6, R^7 is hydrogen,

and their physiologically tolerable salts.

Particularly preferred compounds of the formula I are those in which

R^1 is $-CH_2-OH$, $-CH_3$,

R^4, R^5 are hydrogen,

R^2, R^3, together with the nitrogen to which they are bonded, are a piperazino group, where this piperazino group is substituted in the 4-position by an N,N-dimethylaminosulfonyl group.

US 5,138,058, WO 94/07867, and the scientific literature [e.g. K. Geisen, R. Utz, H. Grötsch, H. J. Lang and H. Nimmesgern, Arzneimittel-Forsch./Drug Res. 44 (II) (1994): 1032 - 1043] describe a large number of pharmacological actions for the compounds of the formula I. Thus, for example, by treatment of diabetic animals with the pyrimidine derivatives of the formula I a significant improvement in the nerve conduction velocity is achieved. Additionally, in the treatment of diabetic rats with the pyrimidines mentioned, a normalization of the glomerular filtration rate and a decrease in albuminuria is observed. The effects described in the literature make the compounds useful pharmaceuticals for the prophylaxis and treatment of disorders of the diabetic type, in particular for the prophylaxis and treatment of late diabetic damage.

It has now surprisingly been found that the pyrimidine derivatives of the formula I described in the literature mentioned and the patents indicated are able to decrease or to inhibit completely the development of tumors. Thus the compounds mentioned are already able on their own and without addition of other substances to bring about a favorable therapeutic inhibition, in particular of tumor formation.

Experimental demonstration of the antitumor action

The tumor-prophylactic action of the pyrimidine derivatives of the formula I was tested on rats which had been pretreated with streptozotocin. Streptozotocin is a

methylnitrosourea derivative having alkylating properties. It is an oncogenic and cytotoxic substance which was licensed by the US Food and Drug Administration for the treatment of metastatic islet carcinoma of the pancreas. In rats, a single intravenous bolus injection of streptozotocin leads to the acute occurrence of diabetes mellitus and over a longer period of time to the formation of adenomas and adenocarcinomas of the kidney (Lit of Dr. Geisen VII - XII). In this model of streptozotocin-treated rats, chronic treatment with the pyrimidine derivatives according to the invention leads to the almost complete abolition of the development of renal tumors, whereas 80% of the untreated animals show the formation of adenocarcinomas in the kidneys.

Experimental Example:

24 male rats having a body weight of 210 - 230 g were administered 60 mg/kg of streptozotocin sulfate intravenously for tumor induction. Six weeks after administration of streptozotocin, 12 of the 24 diabetic animals received a dose of 50 mg/kg of 2-methyl-4-(4-N,N-dimethylaminosulfonyl-1-piperazino)pyrimidine orally supplied daily with the drinking water.

After 288 days of treatment, the experiment was ended, 3 animals of the control group and 2 animals of the group treated with 2-methyl-4-(4-N,N-dimethylaminosulfonyl-1-piperazino)pyrimidine dying prematurely. The kidney weight of the control animals was significantly higher than the kidney weight of the animals which received 2-methyl-4-(4-N,N-dimethylaminosulfonyl-1-piperazino)pyrimidine. Only one of ten of the animals treated with 2-methyl-4-(4-N,N-dimethylaminosulfonyl-1-piperazino)pyrimidine had developed a tumor of the size of a lentil in a kidney. In contrast, 7 of the 9 control animals developed pea- to bean-size tumors.

According to the invention, the use of a pyrimidine derivative of the formula I is therefore suitable for the production of a pharmaceutical for the inhibition of tumor growth and for the prevention of tumorigenesis.

The use of a pyrimidine derivative of the formula I for the production of a pharmaceutical for the prevention of oncoses in combination with a therapeutic used in cancer prevention and cancer treatment is preferred.

The use of a pyrimidine derivative of the formula I for the production of a pharmaceutical for the prevention of oncoses in combination with a physical, tumor-therapeutic measure, in particular radiation therapy or hyperthermia therapy, is further preferred.

The use of a pyrimidine derivative of the formula I for the production of a pharmaceutical for the prevention of oncoses in combination with an immunomodulator is likewise preferred.

The use of a pyrimidine derivative of the formula I for the production of a pharmaceutical for the prevention of oncoses in combination with an inhibitor of the cellular sodium-hydrogen exchanger is furthermore preferred.

The use of a pyrimidine derivative of the formula I in combination with other substances which potentiate the action of the pyrimidine derivatives, without themselves having an action directed against tumor formation and tumor growth, for the production of a pharmaceutical for the prevention of oncoses is particularly preferred.

The use of a pyrimidine derivative of the formula I for the production of a pharmaceutical for the prevention of oncoses in combination with pharmacologically tolerable acids or acid-producing nutritive measures is furthermore preferred.

The use of a pyrimidine derivative of the formula I for the production of a pharmaceutical for the prevention of oncoses in combination with modulators of biological pH regulation is furthermore preferred.

The use of a pyrimidine derivative of the formula I for the production of a pharmaceutical for the prevention of oncoses in combination with inhibitors of carboanhydratase is furthermore preferred.

The use of a pyrimidine derivative of the formula I for the production of a pharmaceutical for the prevention of oncoses in combination with an inhibitor of the chloride-bicarbonate exchanger is furthermore preferred.

The use of 2-methyl-4-(4-N,N-dimethylaminosulfonyl-1-piperazino)-pyrimidine and of 2-hydroxymethyl-4-(4-N,N-dimethylaminosulfonyl-1-piperazino)pyrimidine as a pyrimidine component of a tumor therapeutic is very particularly preferred.

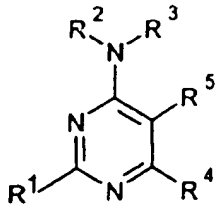
Even on their own without addition of other substances, the pyrimidine derivatives bring about a favorable therapeutic inhibition of tumor growth or of tumor formation.

The relatively low toxic potential of the pyrimidines described here can be combined advantageously with other forms of treatment possible in cancer treatment, and in many cases more toxic, such as, for example,
with chemotherapeutic measures,
with irradiation measures,
with immunomodulators,
with a hyperthermia treatment,
with inhibitors of the cellular sodium-proton exchanger, such as, for example, with amiloride or HOE 642,
with substances which have an inhibitory action on carboanhydratase,
with parallel administration of therapeutically nontoxic and tolerable acids or acid-producing nutritive treatment (such as, for example, the administration of relatively large amounts of glucose/sucrose, e.g. in the form of cola).

The advantage of such a combined treatment can be that the customary more toxic principles of treatment at present (irradiation, chemotherapy, hyperthermia) can be made milder and decreased and/or the antitumor action of a pyrimidine derivative according to the invention can be potentiated.

Patent claims:

1. The use of a pyrimidine derivative of the formula I



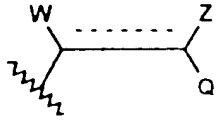
I

in which

R^1 is hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_6-C_{12})-aryl, (C_1-C_6)-alkoxycarbonyl-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-SO-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-SO_2-(C_1-C_6)-alkyl, dihydroxy-(C_1-C_6)-alkyl, aryl, heteroaryl, heteroaryl-(C_1-C_6)-alkyl, aryl-(C_1-C_6)-alkyl, (C_1-C_6)-alkoxycarbonylaryl, aryl-(C_1-C_6)-alkyloxy or heteroaryl-(C_1-C_6)-alkyloxy,

heteroaryl is pyridyl, furyl, tetrahydrofuryl, thienyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, benzothiazolyl;

where aryl and heteroaryl independently of one another can be substituted by one or more substituents selected from the group consisting of chlorine, bromine, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, -SO_2-(C_1-C_6)-alkyl, hydroxy-(C_1-C_6)-alkyl, trifluoromethyl, or

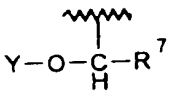
R^1 is  in which the dashed line is an optional double bond;

W, Q, Z independently of one another are H, (C_1-C_6)-alkyl, trifluoromethyl, phenyl, furyl, triazolyl, thiazolyl, thienyl, where phenyl, furyl, triazolyl, thiazolyl, thienyl independently of one another can be mono- to trisubstituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, trifluoromethyl, hydroxyl, or

R^1 is -(C=O)-R^6

R^6 is H, (C_1-C_6)-alkyl, aryl, heteroaryl

heteroaryl is pyridyl, furyl, tetrahydrofuryl, thienyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, benzothiazolyl; where aryl and heteroaryl independently of one another can be substituted by one to three substituents selected from the group consisting of chlorine, bromine, nitro, trifluoromethyl, (C_1-C_6)-alkoxy, -S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, -SO_2-(C_1-C_6)-alkyl, or

R^1 is 

R^7 is aryl, heteroaryl

heteroaryl is pyridyl, furyl, thienyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, quinoyl, where aryl and heteroaryl independently of one another can be substituted by one to three substituents selected from the group consisting of chlorine, bromine, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy,

-S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, -SO_2-(C_1-C_6)-alkyl;

R^2, R^3 independently of one another are hydrogen, (C_1-C_6)-alkyl, (C_6-C_{12})-aryl, (C_6-C_{12})-arylalkyl having 1 - 4 alkyl carbon atoms, where aryl can be substituted by one to three substituents selected from the group consisting of chlorine, bromine, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, or

R^2 and R^3, together with the nitrogen to which they are bonded, form the azetidino, pyrrolidino, piperidino, piperazino or morpholino group, where the heterocycles can be substituted by one or two substituents selected from the group consisting of chlorine, bromine, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, -SO_2-(C_1-C_6)-alkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, (C_1-C_6)-alkoxycarbonyl, N,N-(C_1-C_4)-dialkylcarbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, (C_6-C_{12})-arylcarbonyl substituted in the aryl radical by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_6-C_{12})-arylcarbonyl substituted in the aryl radical by (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_6-C_{12})-arylsulfonyl substituted in the aryl radical by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3, heteroarylcarbonyl or heteroarylsulfonyl;

R^4 and R^5 independently of one another are hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_6-C_{12})-aryl, naphthyl, furyl, where (C_6-C_{12})-aryl, naphthyl and furyl can be substituted by one or two substituents selected from the group consisting of chlorine, bromine, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -S-(C_1-C_6)-alkyl, -SO-(C_1-C_6)-alkyl, -SO_2-(C_1-C_6)-alkyl, hydroxyl;

or its physiologically tolerable salts, for the production of a pharmaceutical for the prevention of tumor formation.

2. The use of a pyrimidine derivative of the formula I as claimed in claim 1, wherein the radicals have the following meaning

R^1 is cyano, trifluoromethyl, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-hydroxyalkyl, $(C_1$-$C_6)$-alkoxy or $(C_6$-$C_{12})$-aryl;

R^4 and R^5 are hydrogen, halogen or trifluoromethyl;

R^2, R^3 independently of one another are hydrogen, $(C_1$-$C_6)$-alkyl, $(C_6$-$C_{12})$-aryl or $(C_6$-$C_{12})$-arylalkyl having 1 - 4 alkyl carbon atoms, or

R^2 and R^3, together with the nitrogen to which they are bonded, form the azetidino, pyrrolidino, piperidino, piperazino or morpholino group, or an azetidino, pyrrolidino, piperidino, piperazino or morpholino group substituted by identical or different groups R^6 and R^7;

R^6, R^7 are $(C_1$-$C_6)$-alkyl, sulfamoyl, N-$(C_1$-$C_4)$-alkylsulfamoyl, N,N-$(C_1$-$C_4)$-dialkylsulfamoyl, $(C_1$-$C_6)$-alkoxycarbonyl, N,N-$(C_1$-$C_4)$-dialkylcarbamoyl, N-$(C_1$-$C_4)$-alkylcarbamoyl, N-$(C_6$-$C_{12})$-arylcarbamoyl, $(C_6$-$C_{12})$-arylcarbamoyl substituted in the aryl radical by $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, halogen, NO_2, NH_2, CN or CF_3, carbamoyl, $(C_1$-$C_6)$-alkylcarbonyl, $(C_6$-$C_{12})$-arylcarbonyl, $(C_6$-$C_{12})$-arylcarbonyl substituted in the aryl radical by $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, halogen, NO_2, NH_2, CN or CF_3, $(C_1$-$C_6)$-alkylsulfonyl, $(C_1$-$C_6)$-alkylsulfinyl, $(C_6$-$C_{12})$-arylsulfonyl, $(C_6$-$C_{12})$-arylsulfonyl, substituted in the aryl radical by $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, halogen, NO_2, NH_2, CN or CF_3, heteroarylcarbonyl or heteroarylsulfonyl or one of the substituents R^6, R^7 is hydrogen,

or its physiologically tolerable salts.

3. The use of a pyrimidine derivative of the formula I as claimed in claim 1, wherein the radicals have the following meaning

R^1 is $-CH_2-OH$, $-CH_3$,

R^4, R^5 are hydrogen,

R^2, R^3, together with the nitrogen to which they are bonded, are a piperazino group, where this piperazino group is substituted in the 4-position by an N,N-dimethylaminosulfonyl group.

4. The use of the combination comprising a pyrimidine derivative of the formula I as claimed in one or more of claims 1 to 3 and a therapeutic used in cancer prevention and cancer treatment for the production of a pharmaceutical for the prevention of oncoses.

5. The use of a pyrimidine derivative as claimed in one or more of claims 1 to 3 for the production of a pharmaceutical for the prevention of oncoses in combination with a physical tumor-therapeutic measure, in particular radiation therapy or hyperthermia therapy.

6. The use of the combination comprising a pyrimidine derivative of the formula I as claimed in one or more of claims 1 to 3 and an immunomodulator for the production of a pharmaceutical for the prevention of oncoses.

7. The use of the combination comprising a pyrimidine derivative of the formula I as claimed in one or more of claims 1 to 3 and an inhibitor of the cellular sodium-hydrogen exchanger for the production of a pharmaceutical for the prevention of oncoses.

8. The use of the combination comprising a pyrimidine derivative of the formula I as claimed in one or more of claims 1 to 3 and other substances which potentiate the action of the pyrimidine derivatives without themselves having an action directed against tumor formation and tumor growth, for the production of a pharmaceutical for the prevention of oncoses.

9. The use of the combination comprising a pyrimidine derivative of the formula I as claimed in one or more of claims 1 to 3 and pharmacologically tolerable acids or acid-producing substances or foodstuffs for the production of a pharmaceutical for the prevention of oncoses.

10. The use of the combination comprising a pyrimidine derivative of the formula I as claimed in one or more of claims 1 to 3 and modulators of biological pH regulation for the production of a pharmaceutical for the prevention of oncoses.

11. The use of the combination comprising a pyrimidine derivative of the formula I as claimed in one or more of claims 1 to 3 and inhibitors of carboanhydratase for the production of a pharmaceutical for the prevention of oncoses.

12. The use of the combination comprising a pyrimidine derivative of the formula I as claimed in one or more of claims 1 to 3 and an inhibitor of the chloride-bicarbonate exchanger for the production of a pharmaceutical for the prevention of oncoses.

13. The use as claimed in one of claims 1 - 10, wherein the compound of the formula I is 2-methyl-4-(4-N,N-dimethylaminosulfonyl-1-piperazino)pyrimidine or 2-hydroxymethyl-4-(4-N,N-dimethylamino-sulfonyl-1-piperazino)pyrimidine.